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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 38/15, 9/08, 9/19

A1

(11) International Publication Number: **WO 99/42125**

(43) International Publication Date: 26 August 1999 (26.08.99)

(21) International Application Number: PCT/GB99/00511

(22) International Filing Date: 18 February 1999 (18.02.99)

(30) Priority Data:
9803448.1 18 February 1998 (18.02.98) GB

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHARMACEUTICAL FORMULATION OF A DIDEMNIN COMPOUND

(57) Abstract

A stable pharmaceutical composition of a didemnin compound, comprises firstly a lyophilised didemnin preparation including water-soluble material and secondly a reconstitution solution of mixed solvents.

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PHARMACEUTICAL FORMULATION OF A DIDEMNIN COMPOUND

The present invention relates to a pharmaceutical formulation, and more particularly a pharmaceutical formulation of a didemnin compound.

THE BACKGROUND

US Patent 5,294,603 to Rinehart claims a pharmaceutical composition comprising a didemnin, in combination with a pharmaceutically acceptable carrier, excipient or diluent. In that patent, extensive results are given for testing for biological activity, notably assay results for cytotoxicity and antiviral activity.

THE PROBLEM

In practice, there are some difficulties in preparing pharmaceutical compositions of didemnin compounds suited for administration to patients, and there is especially a need for a stable parental pharmaceutical dosage form. More specifically, didemnin compounds such as dehydrodidemnin B, also known as aplidine, require mixing with bulking agents, such as mannitol, for optimal,

stable preparation of pharmaceutical dosage forms, in particular lyophilised preparations,

Certain bulking agents for this purpose, such as mannitol, require water for solubilisation, while drugs such as aplidine are poorly soluble in water. However, drug delivery to patients requires resuspending of the lyophilised materials before use.

THE INVENTION

The present invention solves the problem by providing a pharmaceutical composition of a didemnin compound, comprising firstly a lyophilised didemnin preparation including water-soluble materials and secondly a reconstitution solution of mixed solvents. The mixed solvents comprise an aqueous solvent, with the water serving to dissolve the water soluble material and the other solvent serving to dissolve the didemnin compound.

PREFERRED EMBODIMENTS

The pharmaceutical formulation of this invention is typically a stable parental pharmaceutical dosage form suited for reconstitution for administration to patients as an antitumor treatment. The invention solves the problem for drugs such as aplidine, which must be presented as lyophilised mixtures of two or more substances soluble in incompatible solvents. It preferably

provides, separately bottled or otherwise contained, a premixed three component surfactant/alkanol/water mixture of solvents. In order to allow for proper resuspension of such pharmaceutical dosage forms, the separately packaged solvent mixture is provided to be added to the dry lyophilised preparations containing the drug and water soluble substances such as mannitol, before administration for treatment of disease.

Preferred didemnin compounds for the pharmaceutical compositions of this invention include didemnins and didemnin derivatives, such as dehydrodidemnins, nordidemnins, didemnin congeners and didemnin analogs. The present invention is particularly directed at didemnins with limited water solubility, including for example dehydrodidemnin B, also known as aplidine.

The antitumour agent aplidine (dehydrodidemnin B) is a natural occurring cyclic depsipeptide isolated from the Mediterranean runicate *Aplidium albicans*. Aplidine has been characterised by using several chromatographic and spectrometric techniques. Solubility testing showed that aplidine exhibits poor aqueous solubility. Moreover, the long-term stability of aplidine in solution is currently unknown.

The lyophilised didemnin preparation is preferably prepared by freeze drying a didemnin/alkanol/water mix, especially using t-butanol as the alkanol. The alkanol/water mix suitably contains 25 to 60% v/v alkanol. A bulking agent such as mannitol can

also be included, though other conventional water-soluble additives may be included, known to be of utility in the preparation of such lyophilised dosage forms.

The reconstitution solution preferably comprises a surfactant/alkanol/water mix, especially using a nonionic surfactant and ethanol as the alkanol. The surfactant is suitably 10 to 25% v/v of the mix; the alkanol is suitably 10 to 25% v/v of the mix; and the water is suitably 50 to 80% v/v of the mix.

EXAMPLES

Freeze-drying was performed from a 1.0 mg/ml solution aplidine in 40% v/v t-butanol in water for injection ("WFI) containing 25 mg/ml mannitol as bulking agent. Differential scanning calorimetry studies were conducted to determine the freeze-drying cycle parameters. The prototype, containing 1.0 mg aplidine and 25 mg mannitol per vial was found to be the optimal formulation in terms of solubility, length of the freeze-during cycle and dosage requirements.

A solution composed of 15/15/70% (v/v/v) Cremophor EL/ethanol absolute/WFI was found to the optimal reconstitution solution, Cremophor EL being a glycerol-polyethylene glycol ricinoleate available from BASF in Germany.

Dilutions of reconstituted product with normal saline up to 1:200 showed it to be stable for at least 24 hours after preparation. Quality control of the freeze-dried formulation demonstrated that the manufacturing process does not change the integrity of aplidine. Shelf-life data, available thus far, show that the formulation is stable for at least 6 months when stored at +4°C in the dark.

Thus, the preferred aplidine product of this invention is a dual-package containing:

an injection vial containing aplidine 1 mg/vial lyophilized product, and an injection vial containing 2 ml of 15/15/70% (v/v/v) Cremophor EL/ethanol/water as reconstruction solution.

The use of 15/15/70% (v/v/v) Cremophor EL/ethanol/water as reconstitution solution for a lyophilized product is unprecedented. Thus far, the combination of Cremophor EL/ethanol in commercial available products has been used exclusively as solution vehicle (e.g., taxol or cyclosporine).

The development of the Cremophor EL/ethanol/water vehicle provides a potent co-solvent/surfactant system which can be applied as reconstitution solution in future drug formulations and allows the addition of a water soluble bulking agent such as mannitol. Furthermore, by decreasing the relative amount of Cremophor EL, a less toxic vehicle is created.

The manufacturing procedure of the lyophilized product has also a special feature. Normally, freeze-drying of a drug is performed from a drug solution in water. In the case of aplidine, a 40% (v/v) t-butanol/water mixture is preferably used as freeze-drying medium. Although previously described (e.g. rhizoxin), freeze-drying from a 40% t-butanol/water mixture is not common practice.

In conclusion, the combination of lyophilisation of a drug from a t-butanol/water mixture and the subsequent reconstitution of the lyophilized product with 15/15/70% (v/v/v) Cremophor EL/ethanol/water is unique.

CLAIMS:

1. A pharmaceutical composition of a didemnin compound, comprising firstly a lyophilised didemnin preparation including water-soluble material and secondly a reconstitution solution of mixed solvents.

2. A didemnin composition according to claim 1, intended for reconstitution for administration to patients as an antitumor treatment.

3. A didemnin composition according to claim 1 or 2, wherein the didemnin is chosen from didemnins, dehydrodidemnins, nordidemnins, didemnin congeners and didemnin analogs.

4. A didemnin composition according to claim 3, wherein the didemnin compound is aplidine.

5. A didemnin composition according to any preceding claim, wherein the reconstitution solution comprises an alkanol/water mix.

6. A didemnin composition according to claim 5, wherein the reconstitution solution includes a nonionic surfactant.

7. A didemnin composition according to claim 6, wherein the nonionic surfactant is 10 to 25% v/v of the solution; the

alkanol is ethanol and is 10 to 25% v/v of the solution; and the water is 50 to 80% v/v of the solution.

8. A didemnin composition according to any preceding claim, which comprises a vial of lyophilised didemnin preparation including a water-soluble bulking agent, and a separate vial of a premix of non-ionic surfactant/ethanol/water.

9. A method of preparing a pharmaceutical composition of a didemnin compound, which comprises freeze drying a didemnin/water-soluble additive/alkanol/water mix to provide a lyophilised first component, and separately providing an alkanol/water mix as reconstitution solution.

10. A method according to claim 9 wherein the alkanol in the mix is t-butanol.

11. A method according to claim 9 or 10 wherein the amount of alkanol in the alkanol/water mix is 25 to 60% v/v.

INTERNATIONAL SEARCH REPORT

ational Application No
PCT/GB 99/00511

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/15 A61K9/08 A61K9/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 5 462 726 A (N.J. LODGE) 31 October 1995 (1995-10-31) column 5, line 62 - line 66; claims 1-5; example 4	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 July 1999	30/07/1999

Name and mailing address of the ISA	Authorized officer
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Information on patent family members

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